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hyperlipidemia which comprises administering to the subject a polypeptide [which is an agent] comprising the V-domain of sRAGE or a derivative thereof capable of inhibiting an interaction between AGE and RAGE in an amount effective to [prevent] inhibit atherosclerosis in the subject.--

REMARKS

Claims 1-10, 12, 13, 15-27, 29, 30 and 32-46 were pending in the subject application. Applicants have hereinabove canceled claims 6-7 and 40-45 without prejudice or disclaimer to applicants right to pursue the subject matter of these claims in a later-filed application and amended claim 1. Support for this amendment may be found inter alia in the specification as follows: Claim 1: page 7, lines 10-23, page 16, line 35 and page 17, lines 1-8. Claim 1 does not involve any issue of new matter. Therefore, entry of this amendment is respectfully requested such that claims 1-5, 8-10, 12-13, 15-17, 29, 30, 32-39 and 46 will be pending.

Detailed Action

The Examiner stated that the amendment filed February 06, 2002, has been entered. The Examiner stated that the claims 1-10, 12, 13, 15-27, 29, 30, 32-35, and new claims 36-46 are under consideration. The Examiner alleged that newly submitted claims 40-45 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: claims 40-45 are

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allegedly directed to a method of preventing atherosclerosis which comprises administering an antibody or portion thereof capable of binding to RAGE. The Examiner alleged that the invention originally claimed involved administering a polypeptide which comprises the V domain from the soluble receptor for AGE (sRAGE). The Examiner alleged that these inventions are independent and distinct, as the methods use different agents having different structures and functions, and the searches are different and not co-extensive.

The Examiner alleged that claim 1 has been amended to recite administering "an agent" capable of inhibiting an interaction between AGE and RAGE. The Examiner alleged that the invention originally claimed involved administering a polypeptide which comprises the V domain from the soluble receptor for AGE (sRAGE). The Examiner alleged that these inventions are independent and distinct, as the methods use different agents having different structures and functions, and the searches are different and not co-extensive.

The Examiner alleged that since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. The Examiner alleged that accordingly, claims 40-45 are withdrawn from consideration as being directed to a non-elected invention. The Examiner stated that claims 1-10, 12, 13, 15-27, 29, 30, 32-35 and 46 will be examined in part, as they

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apply to the originally presented invention.

Information Disclosure Statement

The Examiner stated that the Information Disclosure Statement (PTO 1449) filed March 12, 2002, has been received and considered.

Claim Objections

The Examiner stated that claim 1 and dependent claims 2-9, 15-18, 36-37 are objected to as reciting "an agent" capable of inhibiting an interaction between AGE and RAGE, which encompasses non-elected subject matter.

In response, applicants respectfully traverse the Examiner's above objection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove amended claim 1 to more particularly point out the applicants claimed invention. Claim 1 now recites as follows:

" A method of inhibiting atherosclerosis in a subject suffering from hyperlipidemia which comprises administering to the subject a polypeptide **comprising the V-domain of sRAGE or a derivative thereof** capable of inhibiting an interaction between AGE and RAGE in an amount effective to inhibit atherosclerosis in the subject" [emphasis added].

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Therefore, claim 1 now recites a polypeptide comprising the V-domain of sRAGE. Applicants contend that amended claim 1 now more clearly recites the claimed agent, i.e. a polypeptide comprising the V-domain of sRAGE or a derivative thereof, and obviates the Examiner's above objection. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this objection.

Rejection under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 1-10, 12-13, 15-18, 36-39 and 46 are under 35 U.S.C. 112, first paragraph, as containing subject matter which was allegedly not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner alleged that the claims are directed to a method of preventing atherosclerosis in a subject suffering from hyperlipidemia. The Examiner alleged that "preventing" is an absolute word, and atherosclerosis depends on many risk factors, as discussed for example in Basha, Am.Heart J., June 1995, 131(6):1192-202, first and second column. The Examiner alleged referred applicants to the rejection in the Office action mailed 6/24/99 (Paper#8), at page 5. The Examiner alleged that furthermore, hyperlipidemia includes different pathologies and different types of lipids involved (see again Basha). The Examiner alleged that in view of the state of art, that atherosclerosis has many causal factors and a viable course of development, and

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considering the lack of guidance and working example about, for example, the stage of the disease at which the administration should be implemented, and which population will be targeted, it is unpredictable if the method claimed will allow for prevention of atherosclerosis, and for which population, and the claims to a method of preventing atherosclerosis are not enabled by the specification.

In response, applicants respectfully traverse the Examiner's above rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove amended claim 1 to more particularly point out the applicants claimed invention. Claim 1 now recite as follows:

" A method of **inhibiting** atherosclerosis in a subject suffering from hyperlipidemia which comprises administering to the subject a polypeptide comprising the V-domain of sRAGE or a derivative thereof capable of inhibiting an interaction between AGE and RAGE in an amount effective to **inhibit** atherosclerosis in the subject" [emphasis added].

Therefore, claim 1 no longer recites the alleged limitation "preventing". Applicants contend that amended claim 1 now more particularly points out the claimed invention and obviates the Examiner's above rejection. Accordingly, applicants respectfully

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request that the Examiner reconsider and withdraw this rejection.

Rejection under 35 U.S.C. §112, second paragraph

The Examiner rejected claim 6 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner alleged that claim 6 is not further limiting claim 1. The Examiner stated that while amending claim 6, applicants must be aware that claims 7 and claims 36 and 37 must be further limiting the claim they depend from.

In response, applicants respectfully traverse the Examiner's above rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove canceled claims 6-7.

In response to the Examiner's comments regarding claims 36-37, applicants contend that claims 36-37 are properly dependent from independent claim 1 under 37 C.F.R. §1.75. Applicants respectfully direct the Examiner to claims 36-37 which recite as follows:

"36. The method of claim 1, wherein the **hyperlipidemia is hypercholesterolemia.**" [emphasis added]

"37. The method of claim 1, wherein the **hyperlipidemia is hypertriglyceridemia.**" [emphasis added]

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Therefore, applicants contend that the terms "hypercholesterolemia" and "hypertriglyceridemia" as recited in claims 36-37 further limit the "hyperlipidemia" recited in claim 1. Accordingly, claims 36-37 are properly dependent from independent claim 1 under 37 C.F.R. §1.75.

Applicants contend that these comments obviate the Examiner's above rejection. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this rejection.

Claim for Priority

The Examiner stated that applicant's claim for priority under 35 U.S.C. §120 is acknowledged. The Examiner alleged that the applications 08/592,070, filed January 26, 1996, and 08/755,235, filed November 22, 1996, upon which priority is claimed fail to provide adequate support under 35 U.S.C. §112 for the claims of this application. The Examiner alleged that applications 08/592,070 and 08/755,235 do not support claims to methods to prevent atherosclerosis, or to inhibit progression of a macrovessel disease, which comprise administering the V-domain of sRAGE.

The Examiner stated that the priority date for this application remains August 05, 1997, which is the filing date of application 08/905,709.

The Examiner stated that applicants arguments have been considered but have not been found persuasive, because the parent applications

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allegedly do not contemplate the interaction of AGE and RAGE, and that reciting that "administering to the subject an agent capable of inhibiting the interaction of an amyloid- β peptide with the receptor for advanced glycation end products treats "diabetes" and "hyperlipidemic atherosclerosis" does not provide support for the specific interaction involving soluble RAGE that is claimed. The Examiner alleged that furthermore, the originally claimed invention is not to a method using any inhibitor of receptor for AGE, but to a method using a specific domain of sRAGE.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that applications 08/592,070, filed January 26, 1996, and 08/755,235, filed November 22, 1996, provide adequate support under 35 U.S.C. §112 for the claims of the present invention, i.e. a method of inhibiting atherosclerosis in a subject suffering from hyperlipidemia by administering a polypeptide comprising the V-domain of sRAGE or a derivative thereof. Specifically, U.S. Serial No. 08/592,070 (hereafter the 070' application) discloses the amino acid sequences of the V-domain of sRAGE and the condition hyperlipidemic atherosclerosis.

In support, the specification of the 070' application recites that "the condition in this embodiment may be diabetes, Alzheimer's Disease, senility, renal failure, **hyperlipidemic atherosclerosis**, neuronal cytotoxicity, Down's syndrome, dementia associated with head trauma, amyotrophic lateral sclerosis, multiple sclerosis or neuronal degeneration" [emphasis added] See page 13, lines 31-35

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and page 14, line 1.

In response to the Examiner's comments regarding a lack of support in the 070' and 235' applications for the V-domain of sRAGE, applicants respectfully direct the Examiner to Table 1, page 29, lines 22-26, of the 070' application which recites the N-terminal amino acid sequence of RAGE, i.e. the V-domain, as follows:

Table 1 - Amino acid sequences of the ≈50kDa GEL BAND AND 30-35 kDa gel band: Comparison to RAGE

RAGE NH ₂ -terminal	DQNITARIGKPLVLNCKGAPKKPPQQLWK ^a
NH ₂ -terminal ≈50kDa gel	DQXITARIGKPLVLNXXGAPKKPPQQLWK(K) ^b
NH ₂ -terminal 30-35 kDa gel band	DQXITARIGKPLVLNXXGAP ^c

Further describing the data of table 1, the specification of the 070' application recites that "based on protein structure deduced from the bovine RAGE cDNA and immunoblotting results (Neeper et al., 1992; Brett et al., 1993), the ≈50 kDa band would most likely correspond to full-length RAGE. The 30-35 kDa band also demonstrated the same **N-terminal sequence** as RAGE, and most likely **represented the extracellular domain of RAGE** which has been observed previously to undergo proteolysis during purification (Schmidt et al., 1992)" [emphasis added] See page 29, lines 32-34 and page 30, lines 1-5.

Therefore, the specification of the 070' application recites the specific condition "hyperlipidemic atherosclerosis" and the first

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30 amino acids comprising the N-terminal sequence or the extracellular domain of RAGE which has been observed previously to undergo proteolysis during purification, i.e. the V-domain of soluble RAGE (sRAGE). Since the claimed invention relates to a method of **inhibiting atherosclerosis in a subject suffering from hyperlipidemia** by administering to the subject a polypeptide **comprising the V-domain of sRAGE** or a derivative thereof, the '070 application provides support for the claims. Thus, the claimed invention is entitled to an effective filing date of January 26, 1996 (i.e. the filing date of the '070 application). Applicants contend that these comments obviate the Examiner's above rejection and respectfully request that the Examiner reconsider and withdraw this rejection.

Rejection under 35 USC §102(e)

The Examiner rejected claims 1-10, 12, 13, 15-27, 29, 30, 32-39 and 46 under 35 U.S.C. §102(e) as being anticipated by Morser, U.S. Patent No. 5,864,018, for the reasons of record. The Examiner alleged that the claims as examined (see page 2 of this Office action) are to methods which comprise administering a polypeptide comprising the V-domain of sRAGE or a derivative thereof capable of inhibiting the interaction of AGE and RAGE. The Examiner alleged that claim 1 has been amended to recite that the method applies to a subject suffering from hyperlipidemia.

The Examiner alleged that Morser teaches peptides like the peptide of SEQ ID No:8, which block the interaction of AGE and sRAGE

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(col.6, lines 41-52 and col.7, lines 13-20). The Examiner alleged that while Morser defines these peptides by their sequence, these peptides constitute in fact fragments of sRAGE of about 10 amino acids in length, located in the V domain of SRAGE (see attached). The Examiner alleged that the peptides of Morser are derivatives of the V-domain of SRAGE, as the specification, at page 8, line 30+, recites that: "The polypeptide may be a derivative of soluble receptor for advanced glycation end products (sRAGE). The Examiner alleged that the polypeptide may be a soluble extracellular portion of a receptor for advanced glycation end product...". The Examiner alleged that he teaches that the soluble peptides of the invention will comprise one or more of the Ig-like domains of the extracellular region of RAGE (col.5, lines 24-28), therefore the soluble extracellular domain (sRAGE), comprising on Ig V and two IgC domains, is envisioned. The Examiner alleged that he teaches that these polypeptides are useful in treating or preventing disorders which result from excessive levels of AGEs (col.19, lines 1-24), in particular in diabetic microvasculopathy, occlusive vascular disorders and atherosclerosis. The Examiner alleged that he teaches therapeutically effective amounts of the polypeptides, and methods of administration (col.19, line 48 continuing through col.20).

The Examiner alleged that while claim 1 has been amended to recite that the method applies to a subject suffering from hyperlipidemia, claims 1-10, 12, 13, 15-27, 29, 30, 32-35 remain rejected, and the newly examined claims 36-39 and 46 are rejected, because this

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disorder and the disorders in the metabolisms of glucose or lipids recited in claims 409, 22-26, and 36-37, are associated with atherosclerosis, diabetes or macrovessel diseases (see for example Basha, Am.Heart J., June 1995, 131(6):1192-202 cited as evidence, at page 1192, col. 1). The Examiner alleged that claims 12-29 are included in the rejection, as the polypeptides of Moser encompass a 10 kilodalton domain of sRAGE.

The Examiner stated that the peptides of SEQ ID No:18, 12, 13 and 5 are also fragments of sRAGE of about 10 amino acids in length, located in the V-domain of SRAGE (see attached), able to block the interaction of AGE and sRAGE. The Examiner stated that no claim is allowed.

In response, applicants respectfully traverse the Examiner's above rejection. The MPEP states that a rejection based on 35 U.S.C. 102(e) can be overcome by perfecting priority under 35 U.S.C. 120 by amending the specification of the application to contain a specific reference to a prior application. Applicants contend that the claimed invention is entitled to a priority date of January 26, 1996 as discussed supra at pages 2 and 10-11. Therefore, since Morser, U.S. Patent No. 5,864,018 is only available as a reference as of August 16, 1996, i.e. after the effective filing date of the claimed invention (January 26, 1996), Morser is not available as a 102(e) reference. Applicants contend that the claimed priority date obviates the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

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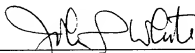
Summary

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of objection and rejection and earnestly solicit allowance of the now pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

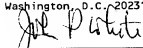
No fee, other than the enclosed \$55.00 fee for a one-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.



8/23/02

John P. White
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Date